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DRAFT – FOR DISCUSSION PURPOSES ONLY

"STRAW PROPOSAL" for DISCUSSION PURPOSES
FRAMEWORK
for a
Voluntary Children's Chemical Evaluation Program[1]

A. Introduction

This document describes EPA's current vision for design of the Voluntary Children's Chemical Evaluation Program (VCCEP). In this program, EPA asks chemical manufacturers to volunteer to sponsor chemicals they produce or import by developing identified needed data in a manner described in this Framework document. This program focuses on chemicals that children are likely to be exposed to. This draft document has been prepared by EPA after careful consideration of all information presented orally and in writing at the September 22, 1999 and November 30 - December 1, 1999 Stakeholders meetings, informal stakeholder meetings, all materials submitted to the associated dockets, and other information available to EPA. This document has been prepared for the April 26-27, 2000 stakeholder meeting to stimulate additional dialogue on policy and technical issues related to this program. The Agency may modify this Framework document based on additional comments received from Stakeholders and the public in connection with the last public Stakeholder meeting.

B. Background -- The Voluntary Children's Chemical Evaluation Program

On April 21, 1998, Vice President Gore, as part of his Chemical Right-to-Know announcement, committed EPA to "....review and report on what new testing may be needed to assess the special impact industrial chemicals may have on children." EPA believes that this initiative's focus is the evaluation of industrial chemicals for their effects on children and prospective parents. In initiating any testing program, decisions need to be made regarding the appropriate chemicals to consider and the appropriate toxicology studies to conduct. To address these issues, EPA initiated a public stakeholder involvement process to bring together individuals with a broad range of interests in children's health issues to provide input, on an individual basis, into the design of a voluntary program to obtain needed test data. Details of this process can be found at www.epa.gov/chemrtk/childhlt.htm.

Project Goal: to take a major first step towards generating chemical hazard and exposure information that can be evaluated to ensure that children are adequately protected from potential risks of industrial and commercial chemicals.

[1]The name of this program has evolved during its development to better reflect the activities it encompasses.

According to this Framework, volunteering to sponsor a chemical that is part of this program requires sponsoring companies to make chemical-specific public commitments to make certain hazard and exposure data publicly available. This commitment is to provide the information needed to make a judgement about the risks to children. It involves a deliberative process and as such is a commitment to conduct only needed tests. Companies will be given an opportunity to sponsor chemicals during the commitment period which will begin during 2000. EPA will consider whether a test rule under section 4 of TSCA is necessary for unsponsored chemicals.

C. Key Program Features

EPA is committed to developing a workable, voluntary testing program for chemicals which children are likely to be exposed. Accordingly, EPA has modified its initial proposals for the program design in several ways. The concepts of tiered testing and exposure assessment are now included as components of the program. However, for such an approach to be acceptable, several program features are essential:

1. All exposure and hazard data developed for this program are to be made publicly available.

2. This program must have a process that moves with some speed to a conclusion. There must be well defined milestones along the way and clear deadlines (e.g., for voluntary commitment, completion of work, etc.) after which the Agency may, where appropriate, use other mechanisms such as rulemaking to develop outstanding data.

3. The initial selection of chemicals should be driven by data that demonstrate a high potential for children's exposure. EPA believes that data indicating presence in human tissues, in food children eat and drink, in children's products, in air (especially indoor air) and in soil and dust should be factors considered in chemical selection. Chemical persistence and bioaccumulation are also relevant factors.

4. Chemicals which may be present in products intended for children's use that result in direct children's exposures (e.g. chemicals present in products that are chewed, mouthed or dermally contacted) are of special concern. An effort to identify the chemicals used in such products would be a very desirable feature of this program.

5. It is important to include consideration of prospective parents' exposures as a secondary factor in chemical selection because such exposures can affect the reproductive health of the parents as well as the development of their children. In addition, the test for reproductive toxicity included in this program includes exposure of parents before conception of their offspring and during prenatal and postnatal development through weaning of their offspring. The test for developmental toxicity includes exposure of the pregnant parent during prenatal development of the fetus.

6. This effort need not be limited to high production volume (HPV) chemicals.

7. One of the recommendations coming out of the peer review conducted by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) of the test battery EPA was contemplating for a proposed rule covering about 50 industrial chemicals (which this voluntary program would supercede) was: "EPA's goal should be to get a consistent set of data on 50 - 60 chemicals where there is reason for special concern, then re-evaluate the value of the tests". The SAP's rationale was that this number of chemicals would provide a sufficient body of data that could be used to reevaluate the test battery and would provide results which could be used to evaluate possible changes to the order in which these studies are conducted in the future. EPA agrees with the SAP's recommendations and rationale.

8. In general, tiering (and specifically triggered testing) can be applied for any number of reasons such as: economic considerations, policy considerations, recognition of scientific or biological knowledge or other reasons. In this case, EPA's analysis, which was supported by the SAP in its review, indicates that the understanding needed to support triggers based on biology does not presently exist. Some stakeholders dispute EPA's analysis and CMA is currently undertaking a retrospective evaluation of well tested chemicals in order to demonstrate that end point specific testing triggers can effectively be incorporated into the testing scheme for this effort. The analyses shared with EPA covered nine chemicals. EPA proposes to apply CMA's retrospective evaluation in the VCCEP as described below.

9. In most instances, HPV Challenge "screening level" data alone will not be sufficient to support dropping a chemical for higher tier testing if there are indicators of high potential exposure. The HPV Challenge battery of tests was designed to help set priorities among a large group of HPV chemicals based on screening level testing. Some studies in the HPV Challenge battery (especially Test Guideline 422 to evaluate repeated dose, reproductive, and developmental toxicity), while useful for priority setting, are not designed to confidently rule out potential hazard concerns for chemicals with large potential exposures. Recognizing this limitation is a key consideration in the design of the VCCEP. New testing under the HPV Challenge for chemicals selected for the VCCEP should be undertaken after careful consideration of the more sophisticated higher tier testing needs of the children's program.

10. Animal welfare considerations are an important element in this program and steps to reduce animal use are encouraged. Such steps include combining studies where possible and adherence to the principles of reduction, replacement and refinement. The maximum use of existing data and applying a tiered testing scheme are important features of this program that will contribute to reducing the number of animals put to test.

11. Given the potential for high exposure associated with the chemicals identified as candidates for the VCCEP (e.g., based on biomonitoring data), EPA believes that this

program should be directed to judging whether potential hazards, exposures and risks to children have been adequately characterized. In making these judgments, EPA believes that the VCCEP is likely to conclude that a full toxicity and exposure evaluation will be needed for each chemical.

12. Hazard data being sought by this program are relevant to an understanding of the inherent toxicological properties of a specific chemical and can be useful in assessing the risks associated with a variety of exposure scenarios. Exposure data, on the other hand, do not represent inherent properties of a chemical and have site- or use- specific relevance. Because of the inherent nature of toxicity data, EPA believes it is important for this program, once it has identified chemicals with a potential for high exposure to children and, as a secondary consideration, prospective parents, to obtain hazard data on those chemicals unless it can be shown via appropriate information that exposures are considerably less than suggested. In the absence of relevant and adequate exposure information, higher tier hazard testing should proceed.

14. A key role of sponsor companies in this effort, in addition to developing hazard data, is to bring forward and assess information on the use and exposures of candidate chemicals included in this effort.

15. EPA believes that the tiered approach should begin with readily available data indicating the potential for high exposure to children (and, as a secondary factor, prospective parents), but which are followed by industry efforts, or the efforts of other stakeholders, to develop more direct quantitative or definitive evidence of exposure to children. Given the starting point of "high potential exposure," EPA believes it would be more protective to use exposure arguments as an element to support dropping chemicals from higher tier testing rather than to use exposure data as a basis for undertaking additional relevant testing.

16. Exposure data developed for this program should include information on exposed populations and routes, frequency, duration and levels of exposure. Furthermore, exposure data must be representative of known exposure scenarios and be of known quality. Exposure assessments should be developed using EPA's Exposure Assessment Guidelines as well as other recognized and accepted exposure assessment procedures and guidance.

17. The VCCEP should not duplicate work conducted under the HPV Challenge Program or activities undertaken as a result of the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC). Activities under VCCEP should be integrated with these and other relevant ongoing programs.

D. Selection of Candidate Chemicals

CMA has urged EPA to select chemicals for this program based on presence in:

- tissues/blood of children,
- food and water children eat and drink,
- air children breathe, including residential or school air,
- products children use, and
- soil and dust in and around residences, schools and daycares.

Stakeholders have also suggested that the tendency of a chemical to persist and bioaccumulate should be an additional consideration in chemical selection. Stakeholders, in their comments to EPA, have indicated support for selecting chemicals for this program based on these criteria.

In an effort to be responsive to stakeholder comments regarding chemical selection, EPA has developed a tool to facilitate the selection of chemicals for this program. This tool is essentially a database which can be used to identify sets of different chemicals derived from various selection criteria and relevant data sources. Thus, the tool allows for consideration of options regarding criteria for chemical selection. A brief description of many of the data sources listed above is provided in Appendix I of this document. Both HPV and non-HPV chemicals are included. Using this tool, EPA believes there is sufficient data at this time to identify chemicals as initial candidates for this program. This Draft Working List of Candidates for the VCCEP and their Chemical Abstract Service (CAS) Numbers are shown in Table 1. These chemicals were selected based on monitoring data demonstrating that they are contained in human tissues, including blood, as reported in at least one of the following datasets:

National Health and Nutrition Examination Survey III (NHANES),
National Human Adipose Tissue Survey (NHATS),
National Human Exposure Assessment Survey (NHEXAS),
Total Exposure Assessment Methodology (TEAM);

and they are believed to be present in foods children eat and drink or in the air children breathe based on monitoring data found in at least one of the following data sources:

FDA database of Everything Added to Food in the United States (EAFUS),
National Contaminant Occurrence Database (includes unregulated drinking water contaminants);
National Human Exposure Assessment Survey (NHEXAS),
Total Exposure Assessment Methodology (Team),
EPA Office of Research and Development studies and other published indoor air data.

Table 1 indicates the source of the biomonitoring data which supports the identification of each candidate chemical. EPA seeks comment on whether biomonitoring data is sufficient by itself to identify candidates for this program and whether the supplementary selection criteria of presence in food, drinking water or indoor air should serve only to identify priority candidates.

All chemicals in Table 1 have been reported to the TSCA Inventory Update Rule and therefore can be presumed to be manufactured and used in the United States.

EPA will endeavor to develop analyses that clarify the current availability of hazard data on chemicals in Table 1 for the April 26-27 Stakeholders'meeting.

A number of chemicals are proposed for deletion from Table 1 because:

- they were not chemicals reported recently to the TSCA Inventory Update Rule,
- they are chemicals being phased out under the Montreal Protocol,
- they are chemicals whose risks to children are believed by EPA to be adequately managed by other ongoing programs,
- they are chemicals selected based on being listed in EAFUS but further investigation has revealed them to be banned for food use, and
- further evaluation of the biomonitoring data source determined that certain chemicals had been monitored for but had not been detected.

Chemicals proposed for deletion are shown in Table 2. EPA seeks comment from stakeholders on all aspects of the selection and deletion of chemicals from the Draft Working List of Candidates for VCCEP.

EPA is aware that several of the chemicals in Table 1 are the subject of ongoing voluntary programs that develop somewhat similar test data and exposure information. Because these ongoing programs are not specific to concerns associated with children, EPA proposes that these efforts continue along with efforts under VCCEP.

While attempting to identify candidate chemicals for this program EPA was able to identify chemicals that are persistent and bioaccumulate but could not find data that clearly indicated a likelihood of children's exposures. Therefore the Draft Working List of Candidates for VCCEP does not include chemicals selected using these criteria.

The National Toxicology Program has recently established the Center for the Evaluation of Risks to Human Reproduction (CERHR). CERHR has formed an expert panel to conduct a detailed review of the toxicology and exposure data for seven phthalates that may be used as plasticizers. The chemical selection criteria being used for VCCEP identifies several of these chemicals as candidate chemicals. However, the following chemicals that are being evaluated by CERHR were not identified as candidate chemicals for VCCEP:

84753	phthalic acid, dihexyl ester
26761400	phthalic acid, diisodecyl ester
28553120	diisononylphthalate
68515480	1,2-benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich
68515491	diisodecyl phthalate.

EPA seeks comment on whether these chemicals should be added to VCCEP because there is an ongoing assessment of their health effects and exposure, and this work could reasonably be integrated into this program and supplemented by efforts of sponsor companies.

Representatives of environmental groups and children's health advocates have urged EPA to consider adding to this program chemicals identified in human breast milk in Sweden[2]. EPA has identified two categories of chemicals covered in the Swedish study that may warrant being included in this program: polychlorinated naphthalenes and polybrominated diphenyl ethers. EPA is in the process of identifying these chemicals' CAS numbers and whether they have been reported to the TSCA Inventory Update Rule, as well as gathering other information relevant to evaluating their candidacy for this program. EPA seeks Stakeholder comment on whether to include these chemicals in the VCCEP.

EPA believes that currently there are inadequate data available to support the selection of chemicals based on their presence in products children use or soil and dust in and around residences. Several Stakeholders have indicated an interest in developing and undertaking an effort to better identify chemicals contained in products designed for children's use. One approach to obtain information on children's products would be for EPA to work with industry to develop this more detailed data. Industry would then collect the data and forward it to EPA in an appropriate electronic format. EPA would be responsible for incorporating the data in a database tool that could be used for priority setting and for making the data accessible to stakeholders. The chemical selection tool being used in the current priority setting effort could accommodate these data. This effort could be extended to address other areas where lack of existing data inhibited the selection on candidate chemicals. An alternative to a voluntary effort to obtain the needed data on children's products would be for EPA to use its authority under TSCA section 8(a). EPA believes efforts to develop this information would be useful to pursue in parallel to the currently proposed approach and would like feedback from stakeholders on how to conduct such an effort.

[2]Noren K., Meironte D. Contaminants in Swedish human milk. Decreasing levels of organochlorine and increasing levels of organobromine compounds. Organohalogen Compounds 38:1-4 (1998).

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Table 1. Draft Working List of Candidate Chemicals to be Addressed by the Voluntary Children's Chemical Evaluation Program. These chemicals have been found in human tissues and may have high exposure potential for children.

CAS	CHEMICAL	HPV	HPV Chall. Commit.	Chemicals found in Human Tissues				Chemicals found In food & Air		
				NHANES	NHAT	NHEXAS	TEAMS	NCOD	EAFUS	INDOOR
62737	dichlorvos	Y			Y					Y
67641	acetone	Y	Y	Y					Y	Y
71432	benzene	Y		Y		Y	Y	Y	Y	Y
75252	tribromomethane						Y	Y		Y
75354	vinylidenechloride	Y	Y				Y	Y		Y
78591	isophorone	Y	Y		Y				Y	
78933	methyl ethyl ketone	Y		Y					Y	Y
79016	trichloroethylene	Y	Y	Y		Y	Y	Y	Y	Y
79345	1,1,2,2-tetrachloroethane	Y	Y				Y	Y		Y
80568	alpha-pinene	Y	Y				Y		Y	Y
84662	diethylphthalate	Y	Y		Y					Y
84742	dibutyl phthalate	Y			Y					Y
85687	butyl benzyl phthalate	Y			Y					Y

Chemical List Clarification

- This list is a preliminary, working list in draft form to be used for discussion purposes only. It does not represent any final decision by EPA on chemicals to be selected for the voluntary program. While care has been taken to accurately generate it, some additional QC is needed and will be performed.
- Additional stakeholder discussions may result in changes to the criteria used to select or remove chemicals from this list.
- No evaluation of the adequacy of existing test data for each of these chemicals has been performed. This will be an initial task of the sponsors participating in the voluntary program. Many of the chemicals are known to be relatively well tested and hence may have only a few test data gaps.

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				NHANES	NHAT	NHEXAS	TEAMS	NCOD	EAFUS	INDOOR
90437	o-phenylphenol	Y			Y					Y
91203	naphthalene	Y	Y		Y			Y		
91225	quinoline				Y				Y	Y
95475	o-xylene	Y		Y			Y	Y		Y
95501	o-dichlorobenzene	Y	Y		Y		Y	Y		Y
95636	1,2,4-trimethylbenzene	Y	Y		Y			Y		Y
98828	isopropylbenzene	Y			Y			Y		Y
100414	ethylbenzene	Y		Y			Y	Y		Y
100425	styrene	Y	Y				Y	Y	Y	Y
103231	diethyl hexyl adipate	Y			Y			Y		
106423	p-xylene	Y					Y	Y		Y
106467	p-dichlorobenzene	Y	Y	Y	Y		Y	Y		Y

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				NHANES	NHAT	NHEXAS	TEAMS	NCOD	EAFUS	INDOOR
106934	ethylene dibromide	Y	Y				Y	Y		Y
107062	ethylene dichloride	Y	Y				Y	Y	Y	Y
108383	m-xylene	Y					Y	Y		Y
108883	toluene	Y		Y			Y	Y		Y
108907	chlorobenzene	Y	Y	Y			Y	Y		Y
112403	n-dodecane	Y	Y				Y			Y
117817	di(2-ethylhexyl)phthalate	Y			Y			Y		Y
117840	di-n-octyl phthalate	Y			Y					
123911	p-dioxane	Y					Y			Y
124185	decane	Y					Y			Y
127184	tetrachloroethylene	Y	Y	Y		Y	Y	Y		Y
128370	2,6-di-tert-butyl-p-cresol	Y	Y		Y				Y	

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				NHANES	NHAT	NHEXAS	TEAMS	NCOD	EAFUS	INDOOR
141935	m-diethylbenzene				Y					Y
142927	hexylacetate				Y				Y	
541731	m-dichlorobenzene	Y	Y		Y		Y	Y		Y
556672	octamethylcyclotetrasiloxane	Y	Y		Y					Y
630206	1,1,1,2-tetrachloroethane	Y	Y				Y	Y		Y
1120214	undecane	Y					Y			Y
1330207	mixed xylenes	Y	Y	Y				Y		Y
5989275	(R)-(+)- p-mentha-1,8-diene	Y	Y		Y				Y	Y

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Table 2. Candidate Chemicals for the Voluntary Children's Chemical Evaluation Program that are proposed for deletion from further consideration under this program.

CAS	CHEMICAL	IUR	Ozone Depletion	Other RM	Not Detected in Biomontorring	Banned Food additive
50293	1,1,1-trichloro-2,2-bis(p-chlorophenyl)-ethane	N				
50328	benzo(a)pyrene	N				
56235	carbon tetrachloride	Y	Y			
56553	benz(a)anthracene	N				
57749	chlordane	N				
58899	lindane (gamma isomer of benzene hexachloride)	N				
60571	1,4:5,8-dimethanonaphthalene,	N				
67663	chloroform	Y		Y		
71556	methyl chloroform	Y	Y			
72208	1,4:5,8-dimethanonaphthalene,	N				
72435	methoxychlor	N				
72548	DDD	N				
72559	1,1-dichloro-2,2-bis(p-chlorophenyl)-ethylene	N				
75274	bromodichloromethane	N				
76448	heptachlor	N				
77474	hexachlorocyclopentadiene				Y	
85018	phenanthrene	N				
87616	1,2,3 trichlorobenzene				Y	
87683	hexachlorobutadiene	N				
91645	coumarin	Y				Y
92524	biphenyl				Y	
96128	1,2-dibromo-3-chloro-propane	N				
108703	1,3,5-trichloro-benzene	N				

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CAS	CHEMICAL	IUR	Ozone Depletion	Other RM	Not Detected in Biomontorring	Banned Food additive
115322	dicofol	N				
118741	hexachlorobenzene	N				
120821	1,2,4 trichlorobenzene				Y	
124118	isononene	N				
124481	dibromochloro-methane	N				
124765	isoborneol				Y	
129000	pyrene	N				
131113	dimethyl phthalate				Y	
206440	fluoranthene	N				
218019	chrysene	N				
309002	1,4:5,8-Dimethanonaphthalene,	N				
319846	alpha-1,2,3,4,5,6- hexachlorocyclohexane				Y	
333415	diazinon	N				
1024573	heptachlor epoxide	N				
1746016	,2,3,7,8-tetrachloro-dibenzo-p-dioxin	N				
2021285	hydrocinnamic acid, ethyl ester	N				
2921882	chlorphyrifos	N				
7439921	lead	Y		Y		
7439976	mercury	Y		Y		
7440382	arsenic	Y		Y		
23184669	butachlor	N				

Table 3 shows selected frequency and concentration data from human monitoring studies that were used to identify candidate chemicals for the Voluntary Children's Chemical Evaluation Program. The information in the table is intended to be illustrative rather than complete. Many of the listed chemicals were also found in other human monitoring studies, some of which report the frequency of occurrence and some of which do not. The blood levels shown in the table are from the National Health and Nutrition Examination Survey (III) (NHANES III); the breath data are from the Total Exposure Assessment Methodology (TEAM) studies; the adipose data are from the National Human Adipose Tissue Survey (NHATS); and the breast milk data are from a recent Swedish study. A number of the candidate chemicals were also studied in the National Human Exposure Assessment Survey (NHEXAS), but these data are not included in the table because all of the chemicals found in NHEXAS were also reported in NHANES III.

With the possible exception of the Swedish breast milk study, all of the monitoring programs from which these data were drawn were relatively large, broad-scale studies. NHANES III was a national-scale program that was able to establish reference levels in blood (e.g. median, 95^{th} percentile) for the nonoccupationally exposed U.S. population for a number of the chemicals studied. NHEXAS involved surveys in EPA Region 5 (MN, WI, MI, IL, IN, OH), in the State of Arizona, and in the Baltimore metropolitan area. NHATS collected data in 47 metropolitan statistical areas. TEAM studies were done in communities in New Jersey, North Dakota, North Carolina, and California. Because of the size and scope of these programs, the detection of a chemical at even a relatively low frequency may indicate exposure to a large population. The significance of the reported tissue concentrations is difficult to interpret without information about the exposure events that led to a chemical's occurrence in that tissue and a detailed knowledge of that chemical's metabolic fate. At present, the reported data are best used simply as a qualitative indicator that exposure has occurred.

The first two substances in the table do not exactly match the corresponding entries on the candidate list. However, EPA believes that the TEAM data on the mixture of meta and para dichlorobenzene are relevant to the listing of m-dichlorobenzene and p-dichlorobenzene as individual isomers and that the NHANES III data on mixed meta and para isomers of xylene are relevant to the listing of m-xylene and p-xylene as individual isomers.

Table 3. ILLUSTRATIVE DATA ON FREQUENCY OF DETECTION AND TISSUE CONCENTRATION FROM HUMAN MONITORING STUDIES

CAS NO.	CHEMICAL NAME	MEDIUM	DETECTION FREQUENCY	CONCENTRATION
	m,p-dichlorobenzene	breath	91% of 49	GM = 1.81 ug/m3
	m,p-xylene	blood	≥ 75% of 649	med = 0.19 ppb
	polybrominated diphenyl ethers	milk		mean = 4 ng/g
	polychlorinated naphthalenes	milk		mean = 0.5 ng/g
62737	dichlorvos	adipose	2%	qualitative only[1]
67641	acetone	blood	≥ 75% of 1062	med = 1800 ppb
71432	benzene	blood	≥ 75% of 883	med = 0.06 ppb
75252	tribromomethane (bromoform)	breath	7% of 90 (500+ other samples without frequency reported)	GM of all samples = 0.67 ug/m3
75354	vinylidene chloride	breath	95% of 49	GM = 6.6 ug/m3
78591	isophorone	adipose	16%	mean = 0.5 ug/g
78933	methylethyl ketone	blood	≥ 75% of 1101	med = 5.4 ppb
79016	trichloroethylene	blood	13% of 677	
79345	1,1,2,2-tetrachloroethane	breath	18% of 67	GM = 0.26 ug/m3
80568	alpha-pinene	breath	92% of 110	GM = 0.94 ug/m3
84662	diethyl phthalate	adipose	10%	mean = 1.7 ug/g
84742	dibutyl phthalate	adipose	76%	mean = 6.1 ug/g
85687	butyl benzyl phthalate	adipose	72%	mean = 5.6 ug/g
90437	o-phenylphenol	adipose	24%	mean = 9.0 ug/g
91203	naphthalene	adipose	84%	mean = 2.0 ug/g
91225	quinoline	adipose	8%	qualitative only[1]
95476	o-xylene	blood	≥ 75% of 711	med = 0.11 ppb
95501	o-dichlorobenzene	breath	13% of 110	GM = 0.06 ug/m3
95636	1,2,4-trimethylbenzene	adipose	62%	qualitative only[1]
98828	isopropylbenzene	adipose	34%	qualitative only[1]

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CAS NO.	CHEMICAL NAME	MEDIUM	DETECTION FREQUENCY	CONCENTRATION
100414	ethylbenzene	blood	≥ 75% of 631	med = 0.06 ppb
100425	styrene	breath	61% of 110	GM = 0.46 ug/m3
103231	diethylhexyl adipate	adipose	10%	qualitative only[1]
106467	p-dichlorobenzene	blood	≥ 75% of 1037	med = 0.33 ppb
106934	ethylene dibromide	breath	3% of 300	GM = 0.4 ug/m3
107062	ethylene dichloride	breath	83% of 300	GM = 1.99 ug/m3
108883	toluene	blood	≥ 75% of 804	med = 0.28 ppb
108907	chlorobenzene	blood	21% of 1024	
112403	n-dodecane	breath	30% of 110	GM = 0.19 ug/m3
117817	di (2-ethylhexyl) phthalate	adipose	78%	mean = 98 ug/g
123911	p-dioxane	breath	8% of 110	GM = 0.05 ug/m3
124185	decane	breath	53% of 110	GM = 0.27 ug/m3
127184	tetrachloroethylene	blood	≥ 75% of 590	med = 0.06 ppb
128370	p-cresol, 2,6-di-tert-butyl-	adipose	18%	mean = 1.1 ug/g
141935	m-diethylbenzene	adipose	8%	mean = 0.6 ug/g
142927	hexyl acetate	adipose	82%	mean = 12.8 ug/g
556672	octamethylcyclotetrasiloxane	adipose	72%	mean = 4.5 ug/g
630206	1,1,1,2-tetrachloroethane	breath	4% of 67 (160 other samples without frequency reported)	GM of all samples = 0.21 ug/m3
1120214	undecane	breath	56% of 110	GM = 0.28 ug/m3
5989275	p-mentha-1,8-diene, (R)-(+)-	adipose	96%	mean = 25.4 ug/g

[1]Qualitative compound monitored only for detection vs. non-detection.

E. Test Battery

EPA has undertaken significant technical efforts to define an appropriate test battery for this program over the last two years. The FIFRA Scientific Advisory Panel and invited members of the EPA Science Advisory Board (SAB) convened in late May 1999 to review the recommendations of the Toxicology Working Group of the 10X Task Force. The Toxicology Working Group had developed recommendations for a core data set necessary to assess the potential hazards to children following exposure to conventional food use pesticides. These recommendations were prepared for consideration in developing the implementation policy for the Food Quality Protection Act's (FQPA) tenfold Safety Factor. EPA's Office of Pollution Prevention and Toxics (OPPT) sought input and advice from this EPA advisory group specifically about the appropriateness of using a selected subset of the 10X battery for a TSCA section 4 test rule addressing chemicals to which children were likely to be exposed. The considerations in the test rule EPA had been planning to propose are similar to those involved in this voluntary program. The SAP's comments were positive with respect to EPA's proposed test battery and therefore EPA is utilizing this test battery as the basis for this voluntary testing program. Furthermore, the SAP supported the application of the battery as a single tier and thought that a program covering about 50 chemicals would provide a sufficient body of data that could be used to reevaluate the battery and provide needed information that could assist in the evaluation of possible changes to the order of tests in the battery in the future. However, during recent Stakeholder discussions, EPA has heard frequently that several of the studies in the test battery should be initiated only after lower level (e.g., HPV Challenge) tests and information indicate cause for concern. In order to meet the needs of as many of the Stakeholders as possible and to ensure the viability of and participation of industry sponsors in a voluntary program, testing tiers have been incorporated in this Framework.

Many of the chemicals selected for this voluntary program will also be HPVs. Hence, the integration of VCCEP and the HPV Challenge Program is very desirable and is incorporated into this Framework.

EPA's experience while developing its test rule also indicates that many of the chemicals likely to be selected for this voluntary program may have been relatively well tested and therefore a significant amount of existing "higher" tier testing will also need to be integrated into this program at its outset.

Recognizing the above science and policy inputs and the key program design features discussed above, EPA believes that a tiering structure may be devised such that:

< the human health effects-related studies included under the HPV Challenge Program serve as the Tier 1 hazard tests in the VCCEP (see Table 4). In addition, any existing higher tier hazard data (as described below) describing a chemical's genetic toxicity, 90-day repeated dose or subchronic toxicity, immunotoxicity, reproductive toxicity, prenatal developmental toxicity, uptake and metabolism, chronic toxicity or carcinogenicity, adult neurotoxicity and developmental neurotoxicity will be considered Tier 1 data in the

VCCEP. If chemicals selected for the VCCEP lack certain Tier 1 tests (specifically, OECD 422 or equivalent data), sponsors should consider conducting appropriate higher tier test(s) given the high exposure potential of these chemicals.

< the studies listed in Table 5 serve as Tier 2 of the VCCEP. The Tier 2 studies go beyond what is needed to fulfill commitments under the HPV Challenge and include: additional genetic toxicity testing (including in vivo studies triggered by activity observed in in vitro tests), 90-day subchronic toxicity, 2-generation reproductive toxicity, prenatal developmental toxicity (two species), immunotoxicity and uptake and metabolism studies. The decision to conduct Tier 2 tests and exposure studies for a specific chemical would be based on a judgement whether the potential hazards, exposures and risks to children have been adequately characterized. The starting point for this assessment would be based on a weight of the evidence-type evaluation of the Tier 1 hazard and exposure data prepared by the sponsor company addressing the chemical's potential for hazards, exposures and risks to children and prospective parents. Existing higher tier data will also be included in this evaluation.

< the studies listed in Table 6 serve as Tier 3. Tier 3 includes tests addressing the following endpoints: chronic toxicity or carcinogenicity, adult neurotoxicity and developmental neurotoxicity. Similarly, the decision to conduct Tier 3 tests for a specific chemical would be based on a judgement whether the potential hazards, exposures and risks to children have been adequately characterized. The starting point for this assessment would be based on a weight of the evidence-type evaluation of the Tier 1 and 2 hazard and exposure data prepared by the sponsor company addressing the chemical's potential for hazards, exposures and risks to children and prospective parents. If the Tier 1 and Tier 2 data were believed to adequately characterize a chemical's potential risks to children, Tier 3 testing would not be pursued.

< Some Stakeholders have questioned the status of validation of the developmental neurotoxicity study. Appendix II provides a detailed explanation of EPA' understanding regarding these issues.

< Stakeholders have also questioned whether studies conducted on adult animals -- the cancer study, the immunotoxicity study and the adult neurotoxicity study -- yield results relevant to understanding a chemical's health effects on children. This issue was raised to the FIFRA SAP during the review of the 10X Toxicology Report. In the report it states the following: "This core data set includes adult as well as developmental toxicity studies for several reasons. For example, adult data are important in delineating target organs that may also be affected when exposures occur in children whose major organ systems have already formed but are functionally less mature than in adults. Since children include adolescents up to 18-21 years of age, adult data will provide important information about potential target organs during this period as well. Adult data also may provide information on target organs to evaluate in the reproduction studies or other developmental studies for similar target organ effects, e.g., developmental

immunotoxicity, developmental carcinogenesis, or endocrine toxicity studies. These targeted studies would then be considered part of the core data set for that chemical. In addition, adult data provide relative potency information in children and adults." The SAP agreed with this and therefore EPA is following their guidance on this matter.

< There may be instances when chemicals included in this program are believed to contact children or prospective parents by multiple routes of exposure and hence testing multiple routes of administration may be needed. CMA, in its proposal, has suggested testing only in the most likely and relevant route of exposure. In some instances, physiologically-based pharmacokinetics (PBPK) testing and modeling may help as an alternative to multiple route testing. EPA proposes that needed studies be conducted by all relevant routes of exposure with, where possible, the alternative of PBPK testing for route to route extrapolation.

< Table 7 shows how the recommended tests under HPV Challenge relate to the Tier 2 and Tier 3 tests included under the VCCEP. It should be noted that the selection of a chemical for the VCCEP would likely impact the new tests a sponsor would conduct to fulfill their HPV Challenge program (Tier 1) commitments. For example, if a chemical which was included in the HPV Challenge Program as well as the VCCEP lacked repeated dose testing data, it would be prudent for the sponsor to conduct a 90 day subchronic study to meet the needs of the VCCEP versus the recommended study under the HPV Challenge program (OECD 422). For information purposes, Table 7 also displays in parenthesis, for selected Tier 2 and Tier 3 tests, the estimated frequency with which an adequate study may not be available to meet the data need. These estimates are based on EPA's experience developing the proposed rule addressing children's chemical testing needs for about 50 similar kinds of chemicals. During the development of this proposal, EPA evaluated, in detail, the adequacy of existing data for the chemicals that were being considered.

Table 4: Tier 1 Studies

HPV Challenge studies relevant to human health effects

Table 5: Tier 2 Studies

Test	Test Guideline
90 day subchronic in rodents	870.3100 (oral) 870.3250 (dermal) 40 CFR 799.9346, 870.346 (inhalation)
reproduction and fertility effects	40 CFR 799.9380, 870.380
prenatal developmental toxicity (two species)	40 CFR 799.9370, 870.370
Triggered off results of HPV Challenge in vitro mammalian chromosomal aberration test: in vivo mammalian bone marrow chromosomal aberrations, OR in vivo mammalian erythrocyte micronucleus	 40 CFR 799.9538, 870.538 40 CFR 799.9539, 870.539
in vitro mammalian cell gene mutation test in L5178Y mouse lymphoma cells	40 CFR 799.9530, 870.530
immunotoxicity	40 CFR 799.9780, 870.780
metabolism and pharmacokinetics	40 CFR 799.9748, 870.748

Table 6: Tier 3 Studies

Test	Test Guideline
carcinogenicity OR chronic toxicity/carcinogenicity	40 CFR 799.9420, 870.420 870.4300
neurotoxicity screening battery	40 CFR 799.9620, 870.620
developmental neurotoxicity	870.6300

Table 7 : The Interrelationships between the HPV Challenge and the Voluntary Children's Chemical Evaluation Program

		Implications on Voluntary Children's Chemical Evaluation Program	
Endpoint	Recommended HPV Challenge (Tier 1) Study	Tier 2 Study	Tier 3 Study
Acute Toxicity	Up and Down Method (OECD 425)	N/A	N/A
Repeated Dose Toxicity	Repeated dose study that also addresses reproductive and developmental toxicity endpoints (OECD 422)	90-day subchronic toxicity study (15%)[3] Recommended HPV Challenge study may not be sufficient	N/A
Reproductive Toxicity	Repeated dose study that also addresses general and developmental toxicity endpoints (OECD 422). OECD 422 is a 1-generation study.	2-generation reproductive toxicity study (70%) Recommended HPV Challenge study may not be sufficient	N/A
Developmental Toxicity	Repeated dose study that also addresses general and reproductive toxicity endpoints (OECD 422)	Testing on two species is needed (50%) Recommended HPV Challenge study does not provide a full evaluation of developmental toxicity, is only conducted on one species and may not be sufficient	N/A

[3]Percentages in parentheses are estimates of the frequency with which the study in question would need to be undertaken in the voluntary program

		Implications on Voluntary Children's Chemical Evaluation Program	
Endpoint	Recommended HPV Challenge (Tier 1) Study	Tier 2 Study	Tier 3 Study
Genetic Toxicity	in vitro gene mutation study in vitro chromosomal aberrations study	additional in vitro study in L5178Y mouse lymphoma cells in vivo studies on micro nucleus or metaphase analysis of bone marrow cells needed if activity observed in HPV Challenge in vitro chromosomal aberrations study	N/A
Immunotoxicity	none	Immunotoxicity study (70%) May be combined with 90-day subchronic study	N/A
Uptake/Metabolism	none	Uptake/Metabolism study (10%)	N/A
Chronic Toxicity/Cancer	none	none	Chronic Toxicity/Cancer study (30%)
Adult Neurotoxicity	none	none	Adult Neurotoxicity study (55%)
Develop. Neurotoxicity	none	none	Developmental Neurotoxicity study (90%)

F. Hazard Information

The sponsor will develop a hazard characterization. This will consist of summaries of all relevant toxicology studies following the guidance for Robust Summaries in the HPV Challenge Program, in the IRIS Toxicological Profiles, or in EPA's risk assessment guidelines. In addition, any additional information, such as mechanistic information or SAR, that may influence decisions on further testing needs should be included.

G. Exposure Information

Although the chemical selection criteria (i.e., biomonitoring data) provide strong qualitative evidence that exposure to the candidate chemicals has occurred, much more information is needed to gain a current understanding of current exposure patterns and levels. The VCCEP will provide sponsor companies opportunities to submit relevant exposure data that will help put hazard data into context. Submission of exposure information to EPA is included as a component in Tier 1, Tier 2 and Tier 3 of the VCCEP. This information will help determine further data needs and, ultimately, will be used in developing risk characterizations for the subject chemicals.

An exposure assessment attempts to answer the following questions for a particular chemical:

- Who and how many people are exposed?
- Does the exposure occur through breathing air, drinking water, eating food, contact with skin or any other routes?
- How much exposure occurs?
- How often and for how long does exposure occur, that is, what is its frequency and duration?

The populations of concern to this program are children and, as a secondary factor, prospective parents. Children can be exposed to chemicals through food and drinking water, through indoor and outdoor air, through ingestion of dust and soil, and through direct contact with products they use and products used in their immediate vicinity. Prospective parents can be exposed to chemicals through these pathways as well as through occupational activities. Although adult exposures are not intended to be a major focus of this program, evaluation of these exposures is part of the overall "weight-of-the-evidence" approach employed in the program. Additionally, certain risks to children, e.g. developmental risks from in utero exposures, can not be assessed without evaluating parental exposures.

The information needed for a complete, transparent exposure assessment should include:

- Identification of all potential manufacturing and processing activities associated with the chemical that can lead to exposure to children or prospective parents
- Identification of all potential uses (industrial, commercial, consumer) of the chemical and activities associated with these uses that may lead to exposure to children or prospective parents

- Identification of all potentially exposed populations with appropriate emphasis on highly exposed and highly susceptible subpopulations
- Measures or estimates of the exposures resulting from the use of the chemical including activities associated with these uses that may lead to exposure
- Measures or estimates of environmental releases from all activities and exposures resulting from these releases
- Identification of relevant activity patterns and age ranges associated with activities that can lead to exposures
- Physical/chemical properties and environmental fate characteristics
- Documentation of all measured data, scenarios, assumptions and estimation techniques

The reporting form developed under the Use and Exposure Information Profile (UEIP) covers much of the basic information listed above and EPA proposes using this form as a starting point for collecting and organizing this information. Similarly, the consumer and commercial product use categories in the proposed TSCA Inventory Update Rule may be a useful starting point for collecting and organizing information on product related exposures

A screening level exposure assessment should generate a conservative, quantitative estimate of exposure. The screening approach generally involves using readily available measured data, existing release and exposure estimates and other exposure-related information. Where actual measures of exposure are not available, simple models, which often use generic scenarios and assumptions, may be used to fill in gaps. For example, a screening-level model for ambient air exposure may use the generic assumption that the exposed populations live near the chemical release locations. A screening level assessment can help to rule out certain exposure concerns and set priorities for more detailed evaluation of the remaining concerns.

Tier 1 exposure information should be screening level (or better) assessments developed using information such as that obtained under the UEIP and supplemented with relevant screening level data on downstream processing and use activities and specific information on children's exposures, if available. Since UEIP was designed to be coupled with SIDS screening level hazard data, EPA believes that an exposure assessment based on UEIP-quality data on all manufacturing, processing, and use activities (particularly if additional data directly relevant to children's exposures is included) may contain sufficient detail to be effectively used with Tier 1 hazard data.

Tier 2 exposure assessments will be more advanced assessments that develop more accurate estimates of exposure and will generally focus on the higher priority exposures identified in the Tier 1 screening assessment. An advanced exposure assessment should quantify central tendency (e.g. median, arithmetic mean) and high end (i.e., greater than 90^{th} percentile) exposures. A representative, well designed monitoring study of known quality is the ideal. Higher tier exposure models may also be used in advanced assessments when appropriate measured data are unavailable. When higher tier models are used, every effort should be made to obtain accurate input data. For example, a higher tier model for ambient air exposure may use

facility-specific parameters for emission rates, such as stack height and the exact size and location of the exposed population. Tier 2 assessments should also more specifically address exposures relevant to Tier 2 health testing endpoints. Similarly, Tier 3 exposure assessments would further develop Tier 1 and 2 exposure data and more specifically address exposures relevant to Tier 3 health testing endpoints.

Exposure assessments should be developed using EPA's Exposure Assessment Guidelines as well as other existing exposure assessment procedures and guidance. EPA and stakeholders will need to work together to develop guidance on the content of exposure assessments for this program so that what constitutes a "complete and conservative" assessment can be better communicated to sponsor companies. Because:

- exposure data will be used in this program to help determine that further testing is not warranted, and
- in the absence of exposure information testing will proceed

sponsor companies will need to be resourceful and bear a special burden in defining and describing the essential exposure issues associated with each chemical included in the program. Because of the strong indicators of human exposure used in selecting chemicals for this program, arguments to discontinue testing based on conclusions of no/low exposure must be supported by convincing analysis and thorough documentation.

H. Risk Characterization

The risk characterization should follow the guidance provided in EPA's risk assessment and exposure assessment guidelines which can be found at www.epa.gov/ncea. The risk characterization should focus on characterizing the hazards, exposures and risks to children and prospective parents, and address the adequacy of the existing data base for this purpose. The risk characterization is intended to summarize key aspects of the following components of the risk assessment:

- qualitative conclusions about the likelihood that the chemicals may pose a specific hazard to children or prospective parents, the nature of the observed effects, under what conditions (route, dose levels, time and duration) of exposure these effects may occur, and whether the health effects-related data are sufficient and relevant to use in a risk assessment.

- A discussion of the dose-response patterns of the effects, the relationship among various endpoints and toxicities, the rationale behind the determination of the NOAEL, LOAEL, and/or benchmark dose, the underlying assumptions, and the implications of using alternative assumptions.

- Descriptions of the estimates of the range of human exposure (e.g., central tendency, high end), the route, duration, and pattern of exposure, relevant

pharmacokinetics aspects, and the size and characteristics of the population exposed. The strengths and weaknesses of the risk assessment.

< The areas of uncertainty and the potential impact on the assessment.

< The potential impact of missing or inadequate hazard or exposure information.

I. Data Needs Assessment

Finally, the sponsor company would prepare a Data Needs Assessment that proposes what additional hazard and/or exposure information is needed to adequately assess the potential risks to children and prospective parents. The sponsor should be familiar with current EPA test guideline requirements and consider to what degree the available hazard information covers current data needs. In situations where adequate data may be lacking for a particular hazard endpoint or for exposure aspects, the sponsor should consider what impact these limitations may have on the ability to adequately characterize the potential hazards, exposures and risks to children. The sponsor should consider Tier 2 (or Tier 3) studies and exposure information needs and use a weight of the evidence type evaluation that integrates both exposure and hazard information to develop recommendations regarding needed work. The sponsor should provide the scientific rationale for any recommended hazard studies beyond those found in the relevant tier (e.g., pharmacokinetics) and for all studies that are not recommended within that tier. In a similar fashion, the sponsor should provide the scientific rationale for the recommendations related to meeting exposure information needs in that tier.

J. Peer Consultation

EPA's Science Policy Council has published the Peer Review Handbook (EPA 100-B-98-001) that provides guidance on formal external peer review and informal peer consultation. Peer consultation provides an opportunity to solicit input and comments from stakeholders on a scientific document. Depending on the nature of the peer consultation, this input could involve an interaction during the development of an evolving work product. Alternatively, it may involve solicitation of comments on a draft document. The key distinctions between peer consultation and formal peer review are the independence of the peer reviewers and their level of involvement. The goal of formal peer review is to obtain an independent, third-party review of a product.

For the VCCEP, the purpose of the peer consultations is to provide a forum for scientists from various stakeholders and relevant outside experts to exchange views on the sponsor's summary document and in particular on the recommended data needs. The peer consultation group will be asked to discuss whether the potential hazards, exposures, and risks to children have been adequately characterized, and to provide scientific input on the hazard and exposure data needs sections. It is not intended to be a consensus based process, but should identify areas of agreement, disagreement, and the supporting scientific rationale.

Peer Consultation Membership

The membership of the peer consultation will vary somewhat for each chemical review. To ensure consistency among reviews, there will be a "core" group that consists of scientists from interested stakeholder groups. This group will be involved in the review of all chemicals. In addition, there will be a group of outside experts that will be invited to participate on a case-by-case basis to provide additional expertise relevant to the specific chemical. This could include experts in specific toxicology disciplines, experts in exposure, or experts in a specific chemical. The peer consultation for a specific chemical will therefore be composed of the core group and any outside experts.

Preparation of the Document for Peer Consultation

The sponsor of the chemical is responsible for preparing the document for peer consultation. The document should consist of four sections. One section should provide robust summaries of all available hazard information (e.g., Tier 1 plus any available Tier 2/3 data) including relevant toxicology studies as well as any additional information (i.e., mechanistic data, SAR) that may influence decisions on data needs. The second section provides and characterizes the exposure information available on this chemical. The third section contains a risk characterization of the chemical and whether the potential hazards, exposures, and risks to children have been adequately characterized. Finally, the last section summarizes the hazard and exposure data needs, as appropriate, in terms of achieving an adequate risk characterization. Recommendations for further work are described along with the scientific rationale, and recommendations for not pursuing additional hazard and/or exposure studies are described along with the scientific rationale. It is also recognized that this section may have a recommendation of low priority for further work, which should also be supported by the scientific rationale.

Guiding Principles for Peer Consultation

The members of the peer consultation group will be given a series of documents that will provide general guidance. This will include EPA's harmonized test guidelines, EPA's risk assessment and exposure assessment guidelines, EPA's risk characterization handbook (which should be finalized soon), CMA's retrospective study, and any additional retrospective analyses that may become available. The peer consultation group will not be given specific rules to follow in their deliberations of data needs as this may restrict their ability to look at the overall picture and bring in as much science as possible.

Conduct of the Peer Consultation

An external, scientifically recognized third party will be responsible for organizing the peer consultation meetings, inviting external experts (Stakeholders will be given an opportunity to suggest appropriate outside experts; selection will be done by the third party), and facilitating the meetings. The sponsor will submit their document to this third party who will be responsible for distributing it to the peer consultation members (core group plus outside experts). The document will also be placed in a public record. The sponsor will present the case to the peer consultation group. The focus of the meetings will be the data needs section of the sponsor's

document.

The meetings will be open to the public. Interested parties who are not part of the peer consultation group will have the opportunity to provide written comments and/or provide verbal comments at the appropriate time during the Peer Consultation meeting.

At the end of the meeting, the recommendations of the peer consultation will be summarized, and distributed to the peer consultation group to check for accuracy. This document, as well as written or verbal comments from outside parties will then be submitted to the sponsor and EPA, and be placed in a public record.

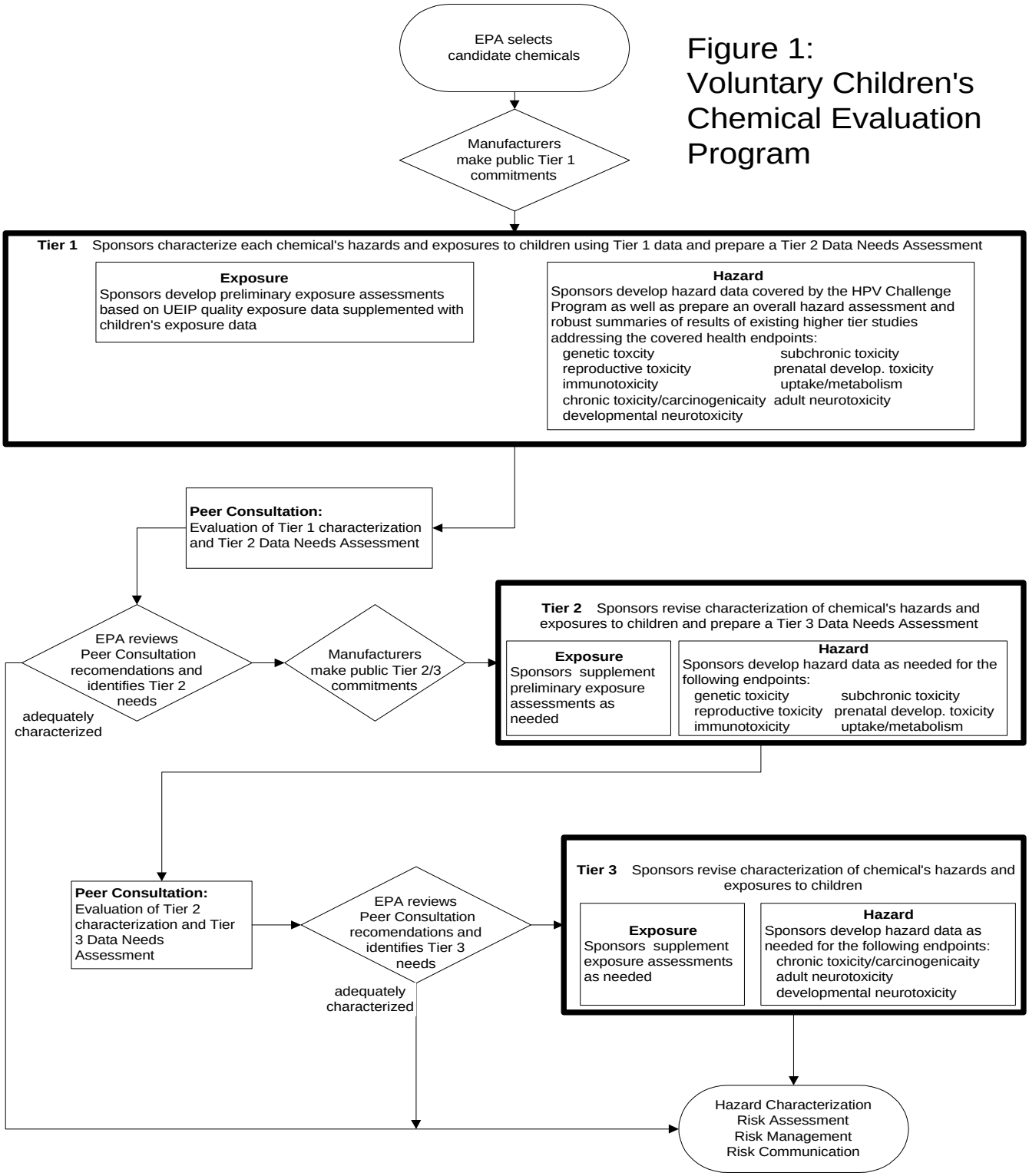
Next Steps After Peer Consultation

This document will be considered by EPA in forming its decisions regarding recommended next steps. If EPA's approach differs from that recommended, it will provide a supporting rationale which indicates the basis for EPA's recommendations.

K. Program Operating Process and Procedures

A schematic applying the points discussed above is shown in Figure 1. The VCCEP is proposed to operate as follows:

Figure 1: Voluntary Children's Chemical Evaluation Program



1. Chemical Selection

After receiving feedback on this Framework document at the April 26-27, 2000 Stakeholder meeting and considering written comments submitted to the docket and other communications, EPA will make a final selection of chemicals for the VCCEP. These chemicals will be those judged by EPA to present, given the data at hand, what are believed to be the relatively greatest potential for exposures that may impact children. EPA will initiate the voluntary program by publishing a Federal Register Notice outlining the program, identifying the chemicals and the test battery, and soliciting sponsorship of specific chemicals by chemical manufacturers and importers.

This voluntary commitment period is proposed to run for 3 months.

2. Tier 1 and Tier 2/3 Commitments and Form of Agreement

To sponsor a chemical at Tier 1, a company (or consortium) would forward a letter to EPA indicating their commitment to handling the chemical under the VCCEP. The letter must identify the chemical by name and CAS number, include a technical contact (and member companies for consortia), and commit to starting development of Tier 1 hazard and exposure data within 6 months of the end of the commitment period. For purposes of the VCCEP, Tier 1 includes the hazard endpoints found in the HPV Challenge as well as any existing Tier 2 or Tier 3 hazard data. Sponsors are encouraged to begin efforts under the VCCEP as soon as practicable but may opt to delay the start year for developing Tier 1 hazard and exposure data to be consistent with the commitment made to the HPV Challenge Program. In these cases, Tier 1 data (as described above) will need to be provided in January of the committed start year. Commitments to participate in the program must be made on a chemical specific basis and include information on start date for VCCEP efforts. Sponsor companies or consortia making a Tier 1 commitment for a specific chemical would agree to:

- sponsor the chemical in Tier 1,
- provide EPA with Robust Summaries of Tier 1 (existing and new studies as needed) studies and existing higher tier hazard studies,
- develop an overall hazard characterization, exposure assessment, and a Data Needs Assessment which describes the higher tier hazard testing and/or exposure data needed to fully characterize the hazards, exposures and risks of the chemical to children.
- make a good faith effort to start and finish all work in a timely manner,
- make all hazard and exposure data developed for this program publicly available ,
- judge existing hazard studies not conducted per Good Laboratory Practices (GLPs) guidelines based on their merits,
- generate new hazard data using GLPs and OPPTS test guidelines,
- develop exposure data that is representative of known exposure scenarios and is of known quality, and
- cooperate with other potential sponsors in facilitating the formation of consortia.

Tier 1 commitments are requested no later than 3 months from the date of the Federal Register Notice announcing the VCCEP. Tier 2/3 commitments are proposed to be made by sponsor companies within 4 months of the issuance of EPA's Tier 2 testing needs decision (which is based on its review of the recommendations provided by the Tier 1 Peer consultation). Some Stakeholders have expressed a preference for a single commitment at the beginning of the program instead of the two commitments proposed above.

In making a Tier 2/3 commitment, the sponsors recognize that they are committing to a process which will undertake to define and obtain needed Tier 3 hazard and exposure data and information.

A sponsor's commitment to the VCCEP represents a way in which a company may voluntarily agree to develop hazard and exposure data on specific chemicals in this program consistent with EPA's Chemical Right-to-Know Initiative. Commitments are not enforceable agreements or contracts. Sponsor companies may withdraw their sponsorship of a chemical at any time with the understanding that EPA may then exercise its authority to require testing under TSCA. Where a chemical is currently being sponsored under VCCEP, the Agency will not simultaneously include such a chemical in a "children's health test rule".

3. Identifying Manufacturers and Importers of Candidate Chemicals

EPA encourages all companies that manufacture or import a selected chemical to share the burdens of this program. When confidential business information (CBI) is not an issue, EPA will assist in identifying the manufacturers and importers.

4. Project Timeline Goals

The proposed timeline goals for this project are as follows:

- publish a Federal Register Notice announcing the program (currently projected to be July-September 2000),
- receive Tier 1 commitments to the Voluntary Children's Chemical Evaluation Program within 3 months of FR publication,
- make all Tier 1 data publicly available within the allowed period for conduct of needed testing (see Table 9 below)
- receive Tier 2/3 commitments within 4 months of EPA's Tier 2 data needs decision,
- make all needed Tier 2 data publicly available within the period for conduct of needed testing,
- make all needed Tier 3 data publicly available within the allotted period.

Table 8: Time Allowed to Conduct Test and Submit Final Report

Test	Months to Submit Final Report[4]
HPV Challenge battery	18[5]
90 day subchronic in rodents	18
reproduction and fertility effects	29
prenatal developmental toxicity (two species)	12
in vivo mammalian bone marrow chromosomal aberrations, OR in vivo mammalian erythrocyte micronucleus	16
in vitro mammalian cell gene mutation test in L5178Y mouse lymphoma cells	12
immunotoxicity	12[6]
metabolism and uptake	12
carcinogenicity OR chronic toxicity/carcinogenicity	60
neurotoxicity screening battery	21
developmental neurotoxicity	21

5. Tracking Sponsor Company Commitments and Performance

[4]Number of months allowed to conduct test and submit the final report after the test sponsor has volunteered to conduct the test.

[5]Less time will be allowed if an adequate OECD 422 (or equivalent) study is already available. Tests within a tier can generally be run concurrently. Sponsors may request an additional 4 months to prepare the Tier 3 Data Needs Assessment.

[6]If the test for immunotoxicity is run as a satellite of another study, the final report would be due on the reporting date of the other study.

Public confidence in the successful outcome of this voluntary program and ongoing participation by the sponsors are both enhanced by the public's ability to follow the program's progress as it occurs. EPA will maintain a database on its web site which will list sponsor company commitments. Information in the tracking database will include:

- the CAS number and name of the chemical,
- the company sponsors and any consortia involved,
- the expected start year for Tier 1 hazard and exposure data development,
- information on results of peer consultations and EPA's data needs recommendations for Tier 2 and Tier 3,
- status of Tier 2/3 commitments, and
- expected and actual years for Tier 2 and Tier 3 submissions to EPA.

6. Submission of Tier 1 Data

Sponsor companies (or consortium) would submit to EPA Robust Summaries of Tier 1 hazard data related to each health endpoint covered by this program in the format used for the HPV Challenge. In addition, along with the Robust Summaries for a sponsored chemical, sponsors would submit an overall characterization of the chemicals hazards, especially to children. Exposure data describing potential exposures would also be submitted. A Data Needs Assessment which would describe additional hazard testing and/or exposure data needed to fully characterize the risks of a chemical to children would also be submitted to EPA.

7. Peer Consultation Regarding Tier 2 Data Needs

EPA would periodically convene a peer consultation to evaluate the Tier 1 Data Needs Assessments and to make specific recommendations for follow up Tier 2 testing and/or exposure information gathering. The peer consultation would also include a review of the robust summaries of Tier 1 hazard data and overall hazard and exposure characterizations. The peer consultation's recommendations would be communicated to EPA.

8. EPA Review of Peer Consultation Results

EPA would review the recommendations of the Peer Consultation, modify them as appropriate, prepare a written Tier 2 Data Needs Decision, mail a copy to the sponsor company, and post the information on its website. If EPA's decision differs substantially from the recommendation of the Peer Consultation, sponsor companies and other stakeholders will have 60 days to comment on EPA's determination regarding Tier 2 data needs. EPA, following consideration of comments, will mail and post its final decision on Tier 2 data needs on its website.

9. Tier 2/3 Commitments

Sponsor companies would have a period of 4 months after it receives EPA's Tier 2 Data Needs Decision to commit to Tiers 2 and 3 of the program. This commitment would be made by letter to the Agency which would contain similar information to that in the Tier 1 commitment letter.

10. Submission of Tier 2 Data

The sponsor company will submit Tier 2 hazard and exposure data in the form of additional Robust Summaries, revised overall hazard characterization, revised exposure data and Tier 3 Data Needs Assessment to EPA. The timeline for this effort would be determined based on the data needs for each chemical using the timelines shown in Table 8.

11. Peer Consultation Regarding Tier 3 Data Needs

EPA would use the same peer consultation arrangement to evaluate whether Tier 2 data needs were met by a sponsor's submission. EPA would periodically convene a peer consultation to evaluate the Tier 3 Data Needs Assessments and to make specific recommendations for Tier 3 testing and/or exposure information gathering. This peer consultation would also evaluate whether the Tier 2 submission fully characterized the chemical's potential hazards to children and whether there were remaining Tier 3 data needs. The peer consultation would also include a review of the robust summaries of Tier 2 hazard data and overall hazard and exposure characterizations. The peer consultation's recommendations would be communicated to EPA.

The peer consultation's recommendations would be submitted to EPA. EPA would review these recommendations, modify them as appropriate, prepare a written description of its Tier 3 Data Needs Decision, mail a copy to the sponsor company, and post the information on its website. If EPA's decision differs substantially from the Peer Consultation recommendation, sponsor companies and other stakeholders will have 60 days to comment on EPA's determination regarding Tier 3 data needs. EPA, following consideration of comments will mail and post its final decision on Tier 3 on its website.

12. Data Dissemination

EPA will make Robust Summaries of hazard data, overall hazard characterizations, exposure data and Data Needs Assessments developed for this program publicly available in a meaningful and accurate way on its web site and by other appropriate means. It will similarly provide access to inputs to and from the peer consultation and EPA's communications with sponsors.

13. Use of Information Submitted and Test Results

All stakeholders to this process will be responsible for contributing to follow up risk assessment, risk management and risk communication actions that result from information developed by this program.

When data and other information generated from this program become available, EPA will

utilize a risk-based, scientifically sound process to make decisions on the need for further information gathering or risk management action. The sponsor company and other stakeholders will be provided adequate notice and a reasonable opportunity to comment should EPA perceive the need to propose risk management actions based on that data.

L. Animal Welfare Considerations

In developing and implementing this program to help meet the goal of protecting children from chemical hazards, EPA has taken several steps in the design of this program that reduce animal testing without unduly compromising the goal of protecting children. EPA is committed to examining alternatives test methods that reduce the number of animals for testing, that reduce the pain and suffering of test animals, and that replace animals in testing with non-animal test systems. Tier 1 of the VCCEP includes testing endpoints found in the HPV Challenge Program and encourages the use of approaches to addressing animal welfare concerns, including the possible use of SAR and category approaches where scientifically justifiable.

A key step in reducing the number of animals used for testing is to ensure maximum use of existing data and to combine tests where feasible.

To ensure the maximum use of existing data, industry and others are encouraged to search for existing relevant and adequate data and to share sources of such information. Sponsor companies will, as part of this program, commit to identifying and assessing the adequacy of existing data. To facilitate this effort, EPA has developed guidance under the HPV Challenge Program and will develop additional guidance for this effort as needed. Sponsors are to consider the feasibility of combining test protocols where it may be possible to reduce the number of animals put to test. Sponsors are encouraged to consider development of PBPK approaches to evaluate route to route extrapolation of test data which also may reduce the number of animals put to test.

One of the most important steps EPA has taken is to use selection criteria for this program which clearly demonstrate that actual exposures to children are likely to be occurring and for which there is a compelling need for children's health effects and exposure data and information to be made publicly available. The resulting list of chemicals for this program displayed in Table 1 are known to relatively well tested. As such, this program has become more structured around data availability and emphasizes the importance of gathering exposure data to support an assessment of the risks of chemicals to children.

The tiered testing design of this program is yet another feature of the program that is responsive to animal welfare concerns. In this program, the Tier 2 and Tier 3 testing will be limited to chemicals for which there is a clear need. As such, Tier 2 and Tier 3 tests will not automatically be required. The need for testing will be considered as part of an overall assessment directed to judging whether the potential hazards, exposures and risks to children have been adequately characterized. This will be done through a deliberative, science-based peer consultation process that is intended to ensure that the testing and exposure information

developed via this program will inform the public on a chemical's potential health effects, exposure and risks to children. The peer consultation process will also serve as a forum for all stakeholders to provide input on the testing needs for each chemical.

The above considerations will receive the most emphasis because unfortunately, with the exception of genetic toxicity, there are few non-animal test methods relevant to this program that have been validated and achieved regulatory acceptance. If relevant test methods become validated and achieve regulatory acceptance during the implementation of the VCCEP, EPA will consider their immediate implementation in the program.

Because the candidate chemicals selected for this effort are believed to have widespread potential for exposures to both children and prospective parents, EPA believes that the availability of the information that will be developed as a result of this program is vitally important so that government, industry and the public can better understand potential chemical hazards, exposures and risks posed to the nation's children.

M. Research and Information Needs Identified by the Stakeholder Process

- < improved test methods using young animals
- < improved test methods which reduce, refine or replace animal testing
- < "day in the life of a child"
- < identification of chemicals in products intended for use by children
- < chemicals in soils and dusts in and around residences, schools and daycares
- < chemicals in air children breathe (indoor and outdoor sources, focusing on children's activity patterns and environments)
- < chemicals identified in human tissues/blood from sources other than those cited above

N. Next Steps

As described above, EPA looks forward to receiving written comments on this Straw Proposal as well as having the benefit of discussions during the April 26-27, 2000 Stakeholder meeting. Following consideration of comments and discussion, EPA will develop and issue a Federal Register Notice outlining the VCCEP (amended as appropriate based on comment), identifying the working list of chemicals and the test battery and tiers, and describing procedures to be applied in implementing the VCCEP, including those related to the Tier 1 and Tier 2/3 voluntary commitment processes.

APPENDIX I

DESCRIPTIONS OF SELECTED DATA

SOURCES FOR CHEMICAL SELECTION TOOL[7]

Pesticide Inerts:

Pesticide inerts found in pesticide products registered by EPA are identified in four alphabetical lists which contain the name, CAS number and List category for each chemical. The Lists of Inert Pesticide Ingredients are compiled by EPA's Office of Pesticide Programs. List 1 identifies those pesticide inerts which are of toxicological concern. There are 8 pesticide inerts on List 1, at least one or more of which is contained in 160 pesticide products. List 2 includes those pesticide inerts which are potentially toxic and have a high priority for testing. There are 64 pesticide inerts on List 2, at least one or more of which is contained in over 9,000 products. List 3 identifies approximately 1500 pesticide inerts whose potential toxicity is unknown. List 4 includes pesticide inerts which are considered to be innocuous.

National Drinking Water Contaminant Occurrence Database:

The National Drinking Water Contaminant Occurrence Database (NCOD) provides data on the occurrence and concentration of unregulated contaminants in drinking water. NCOD was developed to satisfy the statutory requirements set by Congress in the 1996 SDWA amendments. The purpose of the database is to support EPA's decisions related to identifying contaminants for regulation and subsequent regulation development. The NCOD contains occurrence data from both Public Water Systems and other sources (like the U.S. Geological Survey National Water Information System) on physical, chemical, microbial and radiological contaminants for both detections and non-detects.

NCOD contains occurrence monitoring from sampling locations throughout a Public Water System, therefore a detection value does not necessarily mean the contaminant would be found at the tap. There are some summary statistics, but no actual analysis of the data is provided. Also, NCOD contains data for only unregulated contaminants required to be monitored by public water systems, even though EPA has not set health-based drinking water maximum contaminant levels for this subset of contaminants. This subset is covered by the Unregulated Contaminant Monitoring Rule, or UCMR. Currently the NCOD does not contain occurrence data for all water systems and all states. The only Public Water System data contained in NCOD is data that has been reported by States to the Safe Drinking Water Information System (SDWIS). Historical data goes back to 1983.

Food Additives:

The EAFUS (Everything Added to Food in the United States) database is a compilation of various food additives created under an ongoing program known as the Priority-based

[7]Note that some of the databases described in this Appendix were not used to develop the list of chemicals noted in Table 1 of this document. The descriptions included here reflect the data bases currently contained in the draft chemical selection tool.

Assessment of Food Additives (PAFA). This database is maintained by the U.S. Food and Drug Administration (FDA) Center for Food Safety and Applied Nutrition (CFSAN) and contains information regarding ingredients added to food that FDA has approved as direct or indirect food additives, or listed and affirmed as generally regarded as safe (GRAS).

The EAFUS database contains administrative and chemical information for more than 3,000 substances added to food. For 2,000 of those substances, toxicological information is also available. The database contains only a partial list of all food ingredients that may be lawfully added to food due to the fact that under federal law, some ingredients may be added to food under a GRAS determination made independently from FDA. A list of all of the substances in EAFUS is available free of charge at http://vm.cfsan.fda.gov/~dms/eafus.html. The fields available on-line include the name of the chemical, the CAS number, the type of toxicologic information available for the chemical in the EAFUS database, and the CFR citation where the chemical is regulated. The complete database (*Food Additives Toxicology, Regulation, and Properties* by Fergus M. Clydesdale, published December 1996, catalog number 8580), including abstracts of over 7,000 toxicology studies, is available on CD-ROM from CRC Press for $375.

Source Ranking Database:

The Source Ranking Database (SRD), developed by EPA's Office of Pollution Prevention and Toxics, contains formulation or emissions data on 1400 chemicals in approximately 12,000 consumer/commercial products. The formulation/emissions data are used, together with parameters such as building volumes and air exchange rates, amount and duration of product use, and chemical properties, to estimate indoor-air concentrations to which people may be exposed in different environments (the current system defines nine environments). The SRD employs four standard scenarios, based on how products/materials are used indoors, to estimate peak and average indoor-air concentrations in each applicable environment for each chemical in the formulation.

Cosmetic Ingredients

FDA does not have the authority to require manufacturers to register their cosmetic establishments, file data on ingredients, or report cosmetic-related injuries. To keep abreast of such information, FDA initiated a voluntary data collection effort, the Voluntary Cosmetic Registration Program (VCRP). Cosmetic companies that wish to participate in the program forward data to FDA. The regulatory citation establishing the VCRP is in 21 CFR 720. Additional information can be found at http://vm.cfsan.fda.gov/~dms/cos-toc.html

Approximately 2,400 chemicals are listed in the July 1997 version of the VCRP database obtained from FDA. Since the database is maintained under a voluntary program, it should not be considered a complete listing of all cosmetic additives. In addition, FDA

has noted that the database contains information for discontinued as well as currently used cosmetic additives.

Toxics Release Inventory:

The Toxics Release Inventory (TRI) database contains information on the quantity of toxic chemicals released on and off-site into the environment by facilities in the United States that manufacture, import, process, or otherwise use any of the specified chemicals . The TRI, published by the EPA, is a publicly accessible database mandated by Section 313 of the Emergency Planning and Community Right-To-Know Act (EPCRA) and Section 6607 of the Pollution Prevention Act (PPA). Section 313 of EPCRA specifically requires facilities that manufacture, import, process, or otherwise use any of more than 600 designated toxic chemicals in excess of threshold quantities to report releases into the air, water, and land. In addition, off-site transfer information must also be reported.

The program applies to industries in the manufacturing sector and those owned by the federal government; therefore, it does not cover all sources of listed TRI chemicals. In addition, facilities that do not meet the TRI threshold levels (those with fewer than 10 full time employees or those not meeting TRI quantity thresholds) are not required to report.

There are a few known problems in the data collection method with the TRI database. Some facilities may not be fully complying with the reporting requirements either by failing to report at all or reporting for only some of their covered chemicals. In addition, TRI requires the reporting of estimated data and does not mandate that facilities monitor their releases.

EPA ORD Sources of Air Monitoring Data:

The ORD sources consist of eight journal articles and reports that provide data on approximately 400 compounds. Quantitative information on the concentrations and frequency of occurrence of pollutants in ambient and indoor air is available. There are also some quantitative data on the concentrations and frequency of occurrence of pollutants from personal monitoring samples.

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Samfield, EPA-600-R-92-025 (NTIS PB92-158468), 1992. Literature survey of U.S. and foreign indoor concentrations through the late 1980's from residences, office buildings, schools, other commercial buildings.

Brown et al., Indoor Air, 4:123-134, 1994. Comprehensive compilation and analysis of U.S. and European literature, with data on residences, office buildings, schools and other buildings.

NOPES Final Report, EPA/600/3-90/003 (NTIS PB90-152224), January 1990. The Nonoccupational Pesticide Exposure Study is an EPA field study with indoor and outdoor concentrations and I/O ratios from 350 samples taken in homes in Jacksonville, FL and Chicopee-Springfield, MA.

Sheldon et al., "Indoor Pollutant Concentrations and Exposures," California Air Resources Board, contract A833-156, final report, January 1992. A field study of indoor and outdoor concentrations and I/O ratios from 128 homes in Woodland CA.

Shields, et al., Indoor Air, 6:2-17, 1996. A field study of indoor and outdoor concentrations from 70 commercial buildings with different occupant densities.

Daisey et al., Atm. Environ. 28 (22): 3557-3562, 1994. A field study of indoor and outdoor concentrations and I/O ratios from 12 office buildings in northern CA with 3 different types of ventilation systems.

National Human Exposure Assessment Survey:

The National Human Exposure Assessment Survey (NHEXAS) describes the distribution of human exposure to multiple chemicals from multiple routes and sources on a community and regional scale and its association with environmental concentrations and personal activities. NHEXAS focuses on the comprehensive exposure of people to multiple environmental pollutants from multiple routes and sources to address some of the limitations of single-chemical, and single media exposure route studies. To accomplish this, hundreds of subjects were randomly selected from several areas of the country and asked to participate. Researchers measured the levels of chemicals in the air participants breathe; in food, drinking water, and other beverages; and in the soil and dust around their homes. Measurements were also made of chemicals in biological samples (including blood and urine) provided by some participants. Finally, participants completed questionnaires to help identify possible sources of exposure to chemicals. NHEXAS in its fullest sense is a conceptual design which utilizes (a) representative sampling (probability-based sampling of a given population), (b) environmental sampling of air, water, soil/dust, © personal monitoring of air, food and beverages (duplicate diet) and dermal measurements, (d) biomarkers, and (e) questionnaires.

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The EL Sampler: A Press Sampler for the Quantitative Estimation of Dermal Exposure to Pesticides in House Dust, Rufus D. Edwards and Paul J. Lioy, Journal of Exposure Analysis and Environmental Epidemiology, Volume 9, Number 5, September/October 1999, pages 521-529.

Total Exposure Assessment Methodology:

The Total Exposure Assessment Methodology (TEAM) study was designed to develop methods to measure individual total exposure (exposure through air, food, and water) and resulting body burden of toxic and carcinogenic chemicals, and to apply these methods within a probability-based sampling framework to estimate the exposures and body burdens of urban populations in several U.S. cities. The TEAM Study reports the results of eight monitoring studies performed in five communities during different seasons of the year. Breath, personal, outdoor, and water samples were collected for volatile organic compounds. Results of the TEAM Study are reported in a four volume report entitled: The Total Exposure Assessment Methodology (TEAM) Study. Two of the four volumes

provide data in a form that can be incorporated into a priority-setting database. These volumes are: (1) The Total Exposure Assessment Methodology (TEAM) Study: Elizabeth and Bayonne, New Jersey, Devils Lake, North Dakota, and Greensboro, North Carolina: Volume II. Part 2 and (2) The Total Exposure Assessment Methodology (TEAM) Study: Selected Communities in Northern and Southern California: Volume III. Altogether the TEAM Study provides data on about 30 volatile organic compounds from breath, personal air, outdoor air, and water samples.

National Health and Nutrition Examination Survey III (NHANES III):

NHANES III was conducted between 1988 through 1994 on 33,994 people and focused primarily on basic health and nutritional parameters such as blood pressure, immunization status, and nutritional blood measures. NHANES III included a special study that looked at the blood levels of 32 volatile organic compounds (VOCs) in a sample of about 800 volunteers from the overall NHANES study. Eleven compounds were found with high frequency and the data on these 11 compounds were sufficient to establish reference levels (e.g. median, 95th percentile) for the nonoccupationally exposed U.S. population. Another five compounds were found in at least 10% of the samples.

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Ashley et al 1994. Blood Concentrations of Volatile Organic Compounds in a Nonoccupational ly Exposed US Population and in Groups with Suspected Exposure. Clin. Chem. Vol. 40 No. 7, pp. 1401-1404.

National Human Adipose Tissue Survey

The National Adipose Tissue Survey (NHATS) analyzed human adipose (fatty) tissue specimens to monitor human exposure to potentially toxic chemicals. Pathologists and medical examiners from 47 metropolitan statistical areas collected tissue specimens from cadavers and surgical patients during the time period between 1970-1987. These specimens were analyzed for organochlorine pesticides, PCBs, dioxins and furans, volatile organics, semivolatile organics, and trace elements. However, not all compounds were analyzed over the complete time period from 1970 - 1987. Throughout the 1970's and early 1980's the chemical residues of primary interest where organochlorine pesticides and PCBs. During 1982, volatile and semivolatile organic compounds were included in the survey. NHATS was the primary activity of the National Human Monitoring Program (NHMP), operated by the EPA Office of Pollution Prevention and Toxics (USEPA/OPPT), until the early 1990s.

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National Occupational Exposure Survey:

The National Occupational Exposure Survey (NOES) was a nationwide observational survey to identify agents to which workers could be exposed. It was conducted on a sample of nearly 5,000 establishments from 1981-1983. The NOES identified approximately 13,766 chemical, physical, and biological agents. Since the NOES database presents information collected from 1981 through 1983, the data are not necessarily representative of the current number of workers potentially exposed to the identified agents. In addition, the data do not provide actual estimates of exposure. NOES data were also collected to characterize management policy and practice in several areas relating to worker safety and health by both industry type and facility size.

Bioconcentration Factors Data:

Data on Bioconcentration Factors (BCFs) were derived using the BCFWin Model. The Model estimates the BCF based upon chemical structure and log octanol-water partition coefficients. BCFs are available for more than 103,000 chemicals. Because the data were derived from a model and not empirical studies, the data should be viewed as estimates and not actual values.

Environmental Persistence Data:

The Environmental Persistence Data are a compilation of half-life (air, water, soil, sediment) data in units of hours for more than 103,000 chemicals. The data are derived from various models developed by the Syracuse Research Corporation (SRC) and persistence data from The Environmental Modeling Centre's Equilibrium Criterion (EQC) Model. The Environmental Modeling Centre (EMC) was established as part of Environmental and Resource Studies at Trent University, Peterborough, Ontario, Canada in July of 1995. Syracuse Research Corporation (SRC) is an independent, not-for-profit research and development firm chartered by the State of New York. Because the data were derived from models and not empirical studies, the data should be viewed as estimates and not actual values.

The persistence data are derived from the Equilibrium Criterion (EQC) Model, sometimes referred to as the Level 3 Fugacity Model, which is a steady state model using mass transfer coefficients for various media compartments, runoff, deposition, half-life, and other input data to provide general information regarding a chemical's behavior (i.e., partitioning, loss, and transport).

Atmospheric half-lives are derived from the Atmospheric Oxidation Rate Program (AOP), which estimates the reaction rate between organic chemicals and hydroxy radicals. The half-life of a chemical is estimated using an average atmospheric hydroxyl radical concentration and an average atmospheric ozone concentration.

Aqueous half-lives are derived from the Biodegradation Probability Program (BIODEG) using the Ultimate Survey Model output. BIODEG calculates the probability that a chemical under aerobic conditions with mixed cultures of organisms will biodegrade rapidly or slowly. The Ultimate Survey Model was created from the results of a survey of

fifty experts who ranked two hundred organic chemicals on their environmental persistence.

APPENDIX II

Overview of Validation of the Developmental Neurotoxicity Protocol

The studies included in the VCCEP were developed by the EPA or OECD and have all undergone a recognized process involving scientific review and acceptance. Test guidelines are developed by the EPA and the OECD; both use a similar validation and peer review process. In the initial stages of test guideline development, workshops are typically held to review the current scientific knowledge of a particular toxicological or ecotoxicological endpoint. Once a draft test guideline is developed there are two procedures for determining whether the study is valid: (1) through a formal validation study in which multiple laboratories test a series of chemicals using the same protocol to determine the repeatability, relevance and reliability of the methods; or (2) by repeated use over a long period of time during which the method is judged by the scientific community to be valid for the use for which it is intended. Once an EPA test guideline has gone through the appropriate validation, it is further reviewed by the scientific community through a formal public notice and comment period and is reviewed by the EPA's Office of Pesticide Programs Scientific Advisory Panel (SAP). A guideline developed by the OECD receives international peer review. The studies included in the VCCEP have gone through this process.

The test guideline for the developmental neurotoxicity study has been developed over the course of several years. In 1988, a developmental neurotoxicity protocol was developed by the Office of Toxic Substances for the assessment of specific solvents (CFR 795.250). This protocol received extensive scientific review. Several of the test procedures had been validated in earlier studies (e.g., Buekle-Sam et al., 1985). In addition, the Agency held a workshop in April, 1989 entitled "Qualitative and Quantitative Comparability of Human and Animal Developmental Neurotoxicity". Scientists from all sectors attended the workshop, and were assigned to one of four work groups which addressed the following issues: 1) comparability of measures of developmental neurotoxicity in humans and laboratory animals; 2) test methods in developmental neurotoxicity; 3) quantitative evaluation of developmental neurotoxicity data; 4) triggers for developmental neurotoxicity testing. In addition, one of the major issues that the groups were asked to address was the ability of the proposed test guideline to detect agents known to cause developmental toxicity in humans. The conclusion of the workshop participants was that the guideline would detect the neurotoxic effects of each of the agents evaluated, although the specific outcomes might be different than those seen in humans. The results of the workshop were published (Kimmel, Rees, and Francis, 1990).

The proposed guideline was further considered by the SAP in 1989. Based on the results of these scientific reviews, an OPPTS developmental toxicity guideline was published for formal public comment and then finalized in 1991. As part of the OPPTS harmonization process, the guideline was revisited in 1997 and with very slight revisions was published as OPPTS 870.6300.

Recently, some modifications to OPPTS 870.6300 have been suggested by the OECD and

by OPP in its recent Data Call In (DCI) for organophosphate pesticides. The major modification is to extend the dosing period; currently, the dams are dosed from gestation day 6 until postnatal day 10, and one suggestion is to extend this to postnatal day 21. However, this extension raises several issues that do not yet have scientific resolution. To that end, the International Life Sciences Institute (ILSI), in cooperation with EPA, has established a working group of scientists with relevant expertise from government, industry and academia to assemble and evaluate the available science on these issues. Once this is done, the information will be presented at a workshop targeted at the larger scientific community. Depending on the outcome of this activity and the data collected under the DCI, EPA may or may not decide to revise its guideline. It is important to note that this ongoing activity will take years to resolve and that the changes proposed do not "invalidate" the existing guideline.

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